

## **REMARKS**

### **Status of Claims**

The Examiner indicated that the proposed Amendment submitted January 15, 2010 was not entered (Advisory Action dated January 27, 2010), and Applicants request non-entry of that Amendment. Instead, Applicants request entry of the presently submitted amendments and the change of claim status described below is based on changes from the claims submitted in the Response dated July 23, 2009.

Claims 1-4, 11-24 and 29-30 are pending in the application prior to the instant amendments. Claims 1, 11-12, 14, 20 and 22 are currently amended; claims 2-3 and 15-19 are canceled; claims 5-10, 25-28 and 31 were previously canceled; claim 24 is withdrawn from consideration; leaving claims 1, 4, 11-14, 20-23 and 29-30 pending upon entry of the instant amendments in the RCE.

Specifically, as amended herein, claim 1 includes additional limitations including those of original claims 2, 3, 18 and 19 to expedite the prosecution of this case. No new subject matter has been added.

Claim 20 is amended herein to depend from claim 1 due to the cancellation of original claim 3. No new subject matter has been added.

Claims 11-12 and 14, each of which ultimately depends from claim 1, are currently amended to delete subject matter beyond the instantly amended claim 1. No new subject matter has been added.

Claim 22 is currently amended to delete certain subject matter the Applicants are no longer interested in further pursuing.

Applicants believe that all pending claims are in condition for allowance, as discussed in more detail below.

### **Information Disclosure Statement (IDS)**

An IDS form is submitted with this RCE. Applicants respectfully request the Examiner to consider all references on the submitted IDS form and initial these

references. Reference U.S. Patent No. 4,349,558 submitted herein has been cited and considered by the Examiner (Office Action dated Nov. 16, 2009, page 3).

### **Co-pending Applications**

A list of co-pending applications was submitted by the Applicants in the Response filed 7/23/2009.

### **Specification**

No amendment is made to the specification.

### **Rejections under 35 U.S.C. §103(a)**

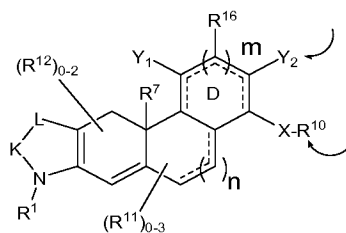
The Examiner rejected claims 1-4, 11-23, 29 and 30 under 35 U.S.C. §103(a) as being obvious over Kumar et al. (J. Med. Chem., 1993, 36, 3278-3285; hereinafter, "Kumar"), Schane et al. (Steroids, 1985, 45(2), 171-85; hereinafter, "Schane") and Bell et al. (US 4,349,558; hereinafter, "Bell"). (Office Action mailed November 16, 2009, page 3) Applicants respectfully traverse this rejection as none of the cited references, either alone or in combination, renders the pending claims obvious.

### **Claims 1, 4, 11-14, 20-23 and 29-30**

The Examiner requested that Applicants disclose the prior art that is related to the provisos in the definitions of Y<sub>2</sub> and Y<sub>3</sub> in the original claim 1 (Office Action dated Nov. 16 2009, first paragraph on page 5). This request is moot in light of the instant amendments.

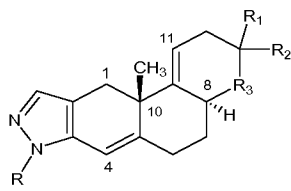
Claim 1 is not obvious over Kumar, Schane and Bell as compounds of claim 1 have substantially different structures from those disclosed by the cited art. None of the references would have provided any reason that would have led a skilled artisan to modify a known compound in the particular manner to arrive at the compounds of claim 1.

Claim 1 has the following general structure wherein Y<sub>2</sub> is CF<sub>3</sub> and R<sup>10</sup> is selected from (1) phenyl, (2) benzyl, and (3) a 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N (wherein each of (1), (2) and (3) is optionally substituted with 1-3 substituents specified in the claim):



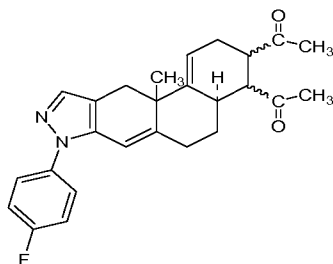
(Claim 1; arrows are added herein for better illustration).

The closest compounds disclosed by Kumar appear to be compounds 8-10 in Table 1 having the following general structure:



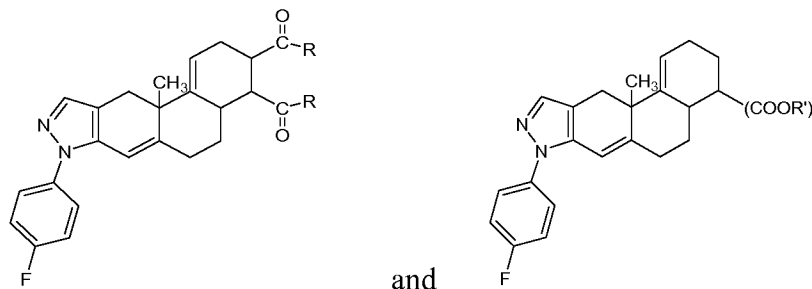
wherein  $R_1$  and  $R_2$  are H or Ac; and  $R_3$  is  $\text{HC}-\text{C}_5\text{H}_4\text{N}$  (Compound 8),  $\text{CHAc}$  (Compound 9) or  $\text{C}(\text{CO}_2\text{Et})_2$  (Compound 10), respectively. (Kumar, Table 1, page 3281)

The closest compound disclosed by Schane has the following structure:



(Schane, Figure 2, WIN 45164, page 173; hereinafter, "Compound 45164")

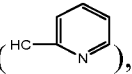
And the closest compounds disclosed by Bell have the following structures:

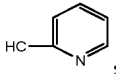


wherein  $R$  and  $R'$  are lower alkyl. (Bell, Abstract)

It can be seen that compounds of claim 1 can be distinguished from those disclosed in Kumar, Schane and Bell on at least two grounds:

First, Y<sub>2</sub> of claim 1 is CF<sub>3</sub>. On the other hand, the structurally closest compounds in Kumar, Schane and Bell have H (compounds 8 and 10 of Kumar), Ac (compound 9 of Kumar); -C(O)CH<sub>3</sub> (compound 45,164 of Schane); and -C(O)R or H (Bell) at the same position (Kumar, Table 1, page 3281; Schane, Figure 2, page 173; and Bell, Abstract).

Second, R<sup>10</sup> of claim 1 is selected from (1) phenyl, (2) benzyl, and (3) a 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N (wherein (1), (2) and (3) can be optionally substituted). In contrast, the structurally closest compounds in Kumar, Schane and Bell have a 6-membered heterocyclic ring ()<sub>2</sub>, Ac and -CO<sub>2</sub>Et (compounds 8, 9 and 10 of Kumar, respectively); -C(O)CH<sub>3</sub> (compound 45,164 of Schane); and -C(O)R or -COOR' (Bell) at the same position.

Therefore it is *not* the case that "[o]ne having ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole" as suggested by the Examiner (Office Action dated Nov. 16 2009, page 4). First, Applicants are unaware of any teaching that would have led a skilled artisan to select the prior art compounds discussed above as lead compounds for further modifications to arrive at claim 1. These compounds were merely disclosed as one of many compounds rather than superior compounds over the other disclosed compounds. Second, there is no teaching in the cited art that would render trivial a change to the D ring that replaces a H, Ac, -C(O)CH<sub>3</sub>, or -C(O)R of the prior art with CF<sub>3</sub> of claim 1 at the Y<sub>2</sub> position. And third, there is no teaching in the cited art to replace , Ac, -CO<sub>2</sub>Et, -C(O)CH<sub>3</sub>, -C(O)R, or -COOR' of the prior art with phenyl, benzyl or a 5-membered HET of claim 1 at the R<sup>10</sup> position.

Courts have consistently held that a *prima facie* case of obviousness *as related to a new chemical compound* requires that the prior art provide some suggestion or motivation for making the specific molecular modifications necessary to achieve the claimed invention combined with a reasonable expectation of success. *Takeda v. Alphapharm*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). The court made it clear that "consistent with the legal principles

enunciated in *KSR*", there must be "some reason that would have led a chemist to modify a known compound in a particular manner." *Id* at 1356-1357.

Moreover, the Federal Circuit case *Eisai* affirmed *Takeda* and further elaborated on the 103 obviousness analysis as related to new chemical compounds. *Eisai v. Dr. Reddy's*, 533 F.3d 1353 (Fed. Cir. 2008). The court stated that "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable". *Id* at 1359. The court further stated that "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with reasoned identification of a lead compound. *Teva* cannot create a genuine issue of material fact on obviousness through the unsupported assertion that compounds other than lansoprazole might have served as lead compounds". *Id*. A very recent case *Teva* further affirmed *Takeda* and *Eisai* as to the 103 obviousness standard. *Proctor & Gamble v. Teva*, CAFC 2008-1404, -1405, -1406 (Fed. Cir. 2009).

Here, the chemical art of the instant application is both unpredictable and vast. The Examiner's generalized assertion that "[o]ne having ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole" (Office Action dated Nov. 16 2009, page 4) is simply unsupported by the teachings of the cited art. As discussed above, there are major structural differences between compounds of claim 1 and the compounds disclosed in the cited art. The cited art does not provide any suggestion or motivation to select the right lead compounds and to make the particular molecular modifications necessary to arrive at the instant compounds.

Moreover, in the absence of any teaching or suggestion of the structural features at the Y<sub>2</sub> and R<sup>10</sup> positions of claim 1 by the cited references, there would be no reasonable expectation of success to obtain compounds of claim 1 by modifying the prior art compounds, both from a synthetic point of view as well as because of known differences between Y<sub>2</sub> and R<sup>10</sup> of claim 1 and those substituents of the cited art at the corresponding positions.

Thus, claim 1 is not obvious over Kumar, Schane and Bell.

Since each of claims 4, 11-14, 20-23 and 29-30 ultimately depends from and includes all limitations of claim 1, these dependent claims also are not obvious over the cited art.

**Claim 22**

Claim 22 is an independent claim and includes a list of specific compounds each of which is structurally different from compounds disclosed in the cited art. The structural feature(s) of claim 22 which are not taught or suggested by the prior art are shown below:

<u>Compound # of Claim 22</u>	<u>Y<sub>2</sub> Substituent</u>	<u>R<sup>10</sup> Substituent</u>
1-81	CF <sub>3</sub>	(Many with additional differences)
82-103 (Deleted)	N/A	N/A
104-140	CF <sub>3</sub>	(Many with additional differences)

For similar reasons as presented above under Claim 1 argument, claim 22 is not obvious over Kumar, Schane and Bell as these references fail to provide any reason that would have led a skilled artisan to select the right lead compounds and then modify the lead compounds in the particular manner to arrive at compounds of claim 22. There would also be no reasonable expectation of success.

In view of the foregoing amendments and remarks, Applicants believe all pending claims are in condition for allowance. Applicants respectfully request withdraw of the §103(a) rejections and allowance of the pending claims.

The Examiner is invited to contact the undersigned attorney at the telephone number provided below if such would advance the prosecution of the instant application. Applicants believe no additional fees are due, but the Commissioner is authorized to charge any fees required in connection with this Response from Merck Deposit Account No. 13-2755.

Respectfully submitted,  
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